Acute Hyperglycemia Impairs Vascular Function in Healthy and Cardiometabolic Diseased Subjects

Systematic Review and Meta-Analysis

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Objectives—Controversy exists over the effect of acute hyperglycemia on vascular function. In this systematic review, we compared the effect of acute hyperglycemia on endothelial and vascular smooth muscle functions across healthy and cardiometabolic diseased subjects.

Approach and Results—A systematic search of MEDLINE, EMBASE, and Web of Science from inception until July 2014 identified articles evaluating endothelial or vascular smooth muscle function during acute hyperglycemia and normoglycemia. Meta-analyses compared the standardized mean difference (SMD) in endothelial and vascular smooth muscle functions between acute hyperglycemia and normoglycemia. Subgroup analyses and metaregression identified sources of heterogeneity. Thirty-nine articles (525 healthy and 540 cardiometabolic subjects) were analyzed. Endothelial function was decreased (39 studies; n=1065; SMD, −1.25; 95% confidence interval, −1.52 to −0.98; $P<0.01$), whereas vascular smooth muscle function was preserved (6 studies; n=144; SMD, −0.07; 95% confidence interval, −0.30 to 0.16; $P=0.55$) during acute hyperglycemia compared with normoglycemia. Significant heterogeneity was detected among endothelial function studies ($P<0.01$). A subgroup analysis revealed that endothelial function was decreased in the macrocirculation (30 studies; n=884; SMD, −1.40; 95% confidence interval, −1.68 to −1.12; $P<0.01$) but not in the microcirculation (9 studies; n=181; SMD, −0.63; 95% confidence interval, −1.36 to 0.11; $P=0.09$). Similar results were observed according to health status. Macrovascular endothelial function was inversely associated with age, blood pressure, and low-density lipoprotein cholesterol and was positively associated with the postocclusion interval of vascular assessment.

Conclusions—To our knowledge, this is the first systematic review and meta-analysis of its kind. In healthy and diseased subjects, we found evidence for macrovascular but not microvascular endothelial dysfunction during acute hyperglycemia. (***Arterioscler Thromb Vasc Biol.* 2015;35:2060-2072. DOI: 10.1161/ATVBAHA.115.305530.)**

Key Words: cardiovascular diseases ■ hyperglycemia ■ meta-analysis ■ microcirculation ■ nitric oxide ■ vascular

The prevalence of type 2 diabetes mellitus represents a major public health issue, directly affecting an estimated 312 million people worldwide.[1] This burden is projected to worsen due, in part, to increasingly sedentary lifestyles and unhealthy dietary habits predominantly characterized by an excess consumption of added sugars.[2–4] Habitual consumption of added sugars, most commonly in the form of sugar-sweetened beverages, is strongly associated with an increased risk in developing type 2 diabetes mellitus, as well as metabolic syndrome and obesity.[5–8] In addition, consumption of added sugars has been linked to an increased risk of developing cardiovascular disease (CVD), which is the leading cause of mortality among those with cardiometabolic disease.[1,9,10] Consumption of excess added sugars leads to acute hyperglycemia, which is considered a better predictor of future CVD events than fasting glycemia in healthy and diabetic populations.[11,12] Indeed, such acute hyperglycemic stress has also been proposed to contribute to vascular dysfunction,[13] which represents one of the main precursors to CVD.[14]

In normal vascular function, the endothelium and vascular smooth muscle (VSM) cells continuously interact to regulate vasodilation and vasoconstriction, maintaining optimal organ perfusion and vascular tone.[15,16] During acute hyperglycemia, increased oxidative stress has been proposed as a key trigger of vascular dysfunction by reducing nitric oxide (NO) production or NO bioavailability.[15,17,18] Furthermore, animal and

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Nonstandard Abbreviations and Acronyms	
CI	confidence interval
CVD	cardiovascular disease
NO	nitric oxide
SMD	standardized mean difference
VSM	vascular smooth muscle

in vitro studies suggest that acute hyperglycemia may also impair VSM function by disrupting VSM cell apoptosis, causing subsequent VSM cell proliferation and desensitization to NO.[19–21] However, whether endothelial and VSM functions are transiently impaired during acute hyperglycemia in humans is unclear because of discrepant results. Given this, we conducted a systematic review and meta-analysis of available studies comparing endothelial function alone or in combination with VSM function during acute hyperglycemia in healthy and cardiometabolic diseased individuals. To our knowledge, this represents the first systematic review and meta-analysis to assess the effect of acute hyperglycemia on vascular function.

Materials and Methods

Materials and methods are available in the online-only Data Supplement.

Results

Study Selection and Characteristics

A flowchart of study selection is shown in Figure 1. The systematic search resulted in the inclusion of 39 from 394 potential articles.[22–60] Fourteen of these articles reported vascular data for multiple subgroups of a given or diverse health status; thus, they were assessed as individual studies.[22,25–28,31,37,38,45,52,56–59] The main characteristics and clinical data for these studies are shown in Tables 1 and 2, respectively. Three potentially relevant studies were not available for full text reading and thus could not be included.[61–63] All studies assessed endothelial or VSM function during acute hyperglycemia and normoglycemia in a total of 1065 individuals classified as healthy (n=525), obese (n=72), impaired glucose tolerance (n=104), type 2 diabetes mellitus (n=229), hypertensive (n=94), metabolic syndrome (n=30), or type 1 diabetic mellitus (n=11).

Quality Assessment and Potential Bias

The quality of the studies was moderate-to-high. The mean score was 9.4±1.5 of possible 12 points (Table 1). The quality of evidence for outcomes demonstrating the effect of acute hyperglycemia on vascular function was low-to-moderate (Table 3). As for the evaluation of potential bias, the funnel plot (Figure 2), Begg and Mazumdar rank correlation test, and the Egger regression test suggested the presence of publication bias or other biases for the standardized mean difference (SMD) in endothelial function in the studies included in the meta-analysis (P<0.01 and P<0.01, respectively). There was no evidence of publication or other biases when assessing the SMD in VSM function in the studies included in the meta-analysis.

Endothelial Function

After data pooling, endothelial function was significantly decreased during acute hyperglycemia compared with normoglycemia (39 studies; n=1065; SMD, −1.25; 95% confidence interval [CI], −1.52 to −0.98; P<0.01; Figure 3). There was no difference between health groups in the SMD in endothelial function (P=0.13), but significant heterogeneity was detected (I^2=87%; P<0.01). Subgroup analysis of the SMD in endothelial function revealed that macrovascular function was significantly decreased during acute hyperglycemia compared with normoglycemia (30 studies; n=884; SMD, −1.40; 95% CI, −1.68 to −1.12; P<0.01), whereas no significant decrease was found in the studies that assessed microvascular endothelial function (9 studies; n=181; SMD, −0.63; 95% CI, −1.36 to 0.11; P=0.09). Heterogeneity was detected in the SMD in endothelial function for both macrovascular (I^2=84%; P<0.01) and microvascular function studies (I^2=90%; P<0.01). Of note, the heterogeneity about microvascular endothelial function was primarily explained (≈40%) by a single study,[30] and the exclusion of such study did not significantly alter the pooled effect size (8 studies; n=147; SMD, −0.18; 95% CI, −0.53 to 0.17; P=0.30).

VSM Function

After data pooling, VSM function was preserved during acute hyperglycemia versus normoglycemia (6 studies; n=144; SMD, −0.07; 95% CI, −0.30 to 0.16; P=0.55; Figure 4). There was no significant difference between health groups in the SMD in VSM function (P=0.49), and no heterogeneity was observed (I^2=0%; P=0.85). Because of limited data availability, it was not possible to analyze macro-VSM and micro-VSM function separately.

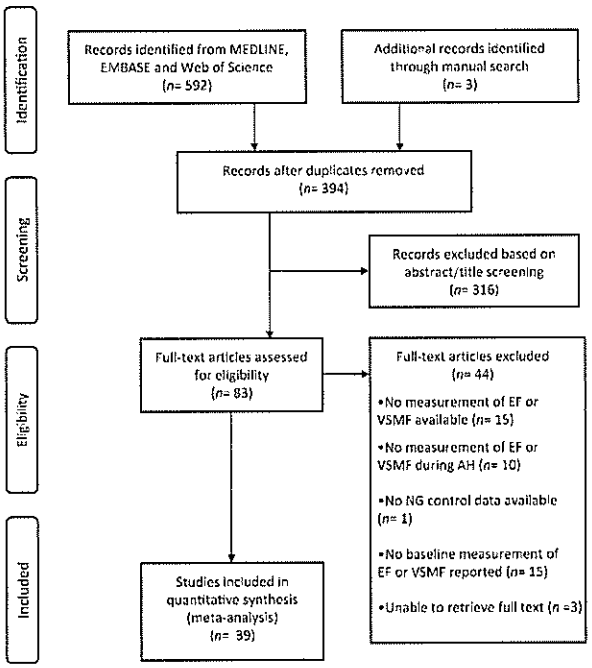

Figure 1. Flow diagram of the study selection process. AH indicates acute hyperglycemia; EF, endothelial function; NG, normoglycemia; and VSMF, vascular smooth muscle function.

Table 1. Main Characteristics of Studies Included in the Meta-Analysis

Study, Year of Publication	Study Design	Health Status	Medication	Quality Score (0–12)	Vascular Region	Inducing AH		Vascular EF During AH	VSMF During AH
						Method	Dose		
Grasser et al,[34] 2014	RCT	Healthy	None	9	Micro	Energy drink	Sucrose/ glucose, 39.1 g	↑ ACh	NA
Nakayama et al,[43] 2013	OBS	Healthy	None	6	Macro	Sugar drink	Maltose, 75 g	↓ FMD	NA
Mah et al,[42] 2013	RCT	Healthy	None	11	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Wang et al A,[52] 2013	RCT	Healthy	None	9	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Zhang et al A,[59] 2013	RCT	Healthy	None	10	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
De Marchi et al,[30] 2012	RCT	Healthy	None	8	Micro	OGTT	Glucose, 75 g	↓ ACh	↔ SNP
Grassi et al,[35] 2012	RCT	Healthy	None	9	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Suzuki et al,[49] 2012	OBS	Healthy	None	8	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Ceriello et al A,[28] 2011	RCT	Healthy	None	6	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Mah et al,[41] 2011	RCT	Healthy	None	11	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Watanabe et al,[53] 2011	OBS	Healthy	None	11	Macro	OGTT	Glucose 75 g	↓ FMD	NA
Baynard et al A,[25] 2009	OBS	Healthy	3 statin, 1 hydrochlorothiazide, 1 angiotensin II receptor blocker, 1 ACE inhibitor	9	Macro	Test meal	Carbohydrate, 80 g	↓ FMD	NA
Ceriello et al (1) A,[27] 2008	OBS	Healthy	None	8	Macro	IV infusion	Glucose, 15 mmol/L	↓ FMD	NA
Ceriello et al (2) A,[28] 2008	RCT	Healthy	None	8	Macro	IV infusion	Glucose, 15 mmol/L	↓ FMD	NA
Natali et al A,[45] 2008	OBS	Healthy	Unknown	11	Micro	OGTT	Glucose, 75 g	↔ ACh	↓ SNP
Weiss et al,[54] 2008	RCT	Healthy	None	10	Macro	Candy/sugar drink	Carbohydrate, 101 g	↓ FMD	NA
Xiang et al (1) A,[57] 2008	RCT	Healthy	None	11	Macro	OGTT	Glucose, 75 g	↔ FMD	NA
Xiang et al (2) A,[58] 2008	OBS	Healthy	None	11	Macro	OGTT	Glucose, 75 g	↓ FMD	↔ NMD
Xiang et al (2) B,[56] 2008	OBS	Healthy	None	11	Macro	OGTT	Glucose, 75 g	↔ FMD	↔ NMD
Dengel et al A,[31] 2007	OBS	Healthy	None	11	Macro	OGTT	Glucose, 75 g	↑ FMD	NA
Zhu et al,[60] 2007	RCT	Healthy	None	7	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Arora et al A,[22] 2006	OBS	Healthy	None	10	Micro	OGTT	Glucose 75 g	↓ PORH	NA
Fujimoto et al,[33] 2006	OBS	Healthy	None	10	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Tushuizen et al,[51] 2006	RCT	Healthy	None	11	Macro	Test meal	Carbohydrate, 55 g	↓ FMD	NA
Napoli et al,[44] 2004	RCT	Healthy	None	6	Micro	Test meal	Carbohydrate, 60 g	↔ ACh	↔ SNP
Siafarikas et al,[47] 2004	RCT	Healthy	None	9	Macro	OGTT	Glucose, 75 g	↔ FMD	NA
Ihlemann et al,[36] 2003	RCT	Healthy	None	7	Micro	OGTT	Glucose, 75 g	↓ Serotonin	↓ SNP
Bagg et al,[23] 2000	RCT	Healthy	None	9	Macro	IV infusion	Dextrose, 10% 238 mL	↔ FMD	NA
Title et al,[50] 2000	RCT	Healthy	None	11	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Kawano et al A,[38] 1999	OBS	Healthy	None	10	Macro	OGTT	Glucose, 75 g	↔ FMD	NA
Williams et al,[55] 1998	OBS	Healthy	None	10	Micro	IV infusion	Glucose, 16.7 mmol/L	↔ Metacholine	NA
Lavi et al,[40] 2009	RCT	Obese	None	8	Macro	Sugar drink	Glucose, 50 g	↓ FMD	NA
Dengel et al B,[31] 2007	OBS	Obese	None	11	Macro	OGTT	Glucose, 75 g	↑ FMD	NA
Wang et al B,[52] 2013	RCT	IGT	None	9	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Natali et al B,[45] 2008	OBS	IGT	Unknown	11	Micro	OGTT	Glucose, 75 g	↔ ACh	↓ SNP
Xiang et al (1) B,[57] 2008	RCT	IGT	None	11	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Arora et al B,[22] 2006	OBS	IGT	None	10	Micro	OGTT	Glucose, 75 g	↓ PORH	NA
Kawano et al B,[38] 1999	OBS	IGT	None	10	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Wang et al C,[52] 2013	RCT	T2DM	None	9	Macro	OGTT	Glucose 75 g	↓ FMD	NA

(*Continued*)

Table 1. Continued

Study, Year of Publication	Study Design	Health Status	Medication	Quality Score (0–12)	Vascular Region	Inducing AH		Vascular EF During AH	VSMF During AH
						Method	Dose		
Ceriello et al B,[26] 2011	RCT	T2DM	6 metformin discontinued 4 wk before 5 excluded ACE inhibitors	6	Macro	OGTT	Glucose 75 g	↓ FMD	NA
Chittari et al,[29] 2011	OBS	T2DM	17 oral agents	10	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Kato et al A,[37] 2010	RCT	T2DM	None	9	Macro	Cookie	Carbohydrate, 75 g	↓ FMD	NA
Kato et al B,[37] 2010	RCT	T2DM	None	9	Macro	Cookie	Carbohydrate, 75 g	↓ FMD	NA
Kato et al C,[37] 2010	RCT	T2DM	None	9	Macro	Cookie	Carbohydrate, 75 g	↓ FMD	NA
Ceriello et al (1) B,[27] 2008	OBS	T2DM	None	8	Macro	IV infusion	Glucose 15, mmol/L	↓ FMD	NA
Ceriello et al (2) B,[26] 2008	RCT	T2DM	None	8	Macro	IV infusion	Glucose 15, mmol/L	↓ FMD	NA
Ceriello et al (2) C,[26] 2008	RCT	T2DM	None	8	Macro	IV infusion	Glucose 10, mmol/L	↓ FMD	NA
Ceriello et al (2) D,[26] 2008	RCT	T2DM	None	8	Macro	IV infusion	Glucose 10, mmol/L	↓ FMD	NA
Natali et al C,[45] 2008	OBS	T2DM	Unknown	11	Micro	OGTT	Glucose, 75 g	↔ ACh	↓ SNP
Stirban et al,[48] 2006	RCT	T2DM	13 insulin, 11 aspirin, 9 ACE inhibitors, 1 angiotensin receptor blocker, 6 hydroxymethylglutaryl-CoA inhibitors, 5 β-blockers, 5 diuretics, 3 calcium channel blockers	11	Macro	Test meal	Carbohydrate, 48 g	↓ FMD	NA
Kim et al,[39] 2003	OBS	T2DM	None	9	Micro	IV infusion	Glucose, 12/mg/kg per min	↓ PORH	NA
Kawano et al C,[38] 1999	OBS	T2DM	None	10	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Shige et al,[46] 1999	OBS	T2DM	None	8	Macro	Test meal	Sucrose, 75 g	↓ FMD	↔ NMD
Zhang et al B,[59] 2013	RCT	Hypertensive	None	10	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Zhang et al A,[58] 2012	RCT	Hypertensive	None	11	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Zhang et al B,[58] 2012	RCT	Hypertensive	None	11	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Ballard et al,[24] 2013	RCT	MetS	None	11	Macro	Rice milk	Mixed sugars, 23 g	↓ FMD	NA
Baynard et al B,[25] 2009	OBS	MetS	3 metformin, 2 sulfonylurea, 4 statin	11	Macro	Test meal	Carbohydrate, 80 g	↓ FMD	NA
Dye et al,[32] 2012	OBS	T1DM	Insulin monotherapy	9	Micro	IV infusion	Dextrose, 200 mg/dL	↓ PORH	NA

Some studies presented multiple health groups comparing normoglycemia and acute hyperglycemia vascular function and were therefore evaluated as individual studies (distinguished by A, B, C, or D). Authors who published multiple studies in a single year were distinguished by (1) or (2). ↓ indicates significant decrease of vascular function during acute hyperglycemia compared with normoglycemia; ↔, no significant difference in vascular function between acute hyperglycemia and normoglycemia; ↑, significant increase of vascular function during acute hyperglycemia compared with normoglycemia; ACE, angiotensin-converting enzyme; ACh, acetylcholine; AH, acute hyperglycemia; EF, endothelial function; FMD, flow-mediated dilation; IGT, impaired glucose tolerance; IV, intravenous; MetS, metabolic syndrome; NA, vascular data not available; NMD, nitroglycerin-mediated dilation; OBS, observational study; OGTT, oral glucose tolerance test; PORH, postocclusive reactive hyperemia; RCT, randomized controlled trial; SNP, sodium nitroprusside; T1DM, type 1 diabetic mellitus; T2DM, type 2 diabetic mellitus; and VSMF, vascular smooth muscle function.

Metaregression Analyses

The SMD in macrovascular endothelial function was inversely associated with age (β=−0.03; P<0.01), systolic blood pressure (β=−0.04; P<0.01), diastolic blood pressure (β=−0.05; P<0.01), mean arterial pressure (β=−0.05; P<0.01), and low-density lipoprotein cholesterol (β=−0.93; P<0.01; Figure 5). In turn, the SMD in macrovascular endothelial function was positively associated with the postocclusion interval of vascular assessment (β=0.36; P=0.01).

Table 2. Clinical Data for Each Study Included in This Meta-Analysis

Study, Year of Publication	Health Status	n (% Women)	Age, y	BMI, kg/m²	Blood Pressure, mm Hg			Fasting Plasma Insulin, pmol/L	Fasting Plasma Glucose, mmol/L	HbA_{1c}, %	Cholesterol, mmol/L			Triglycerides, mmol/L
					SBP	DBP	MAP				Total	HDL	LDL	
Grasser et al,[34] 2014	Healthy	25 (48)	22.5±3	23.3±10	114±10	87±5	96±7	NA	NA	NA	NA	NA	NA	NA
Nakayama et al,[43] 2013	Healthy	23 (0)	44±10	23±2.1	111±8	71±6	84±7	NA	5.1±0.4	NA	NA	NA	NA	NA
Mah et al,[42] 2013	Healthy	16 (0)	21.8±3.2	24.8±NA	117±4	79±4	92±4	142.5±94.4	5.3±0.4	NA	3.7±0.8	NA	NA	3.3±5
Wang et al A,[52] 2013	Healthy	33 (64)	51.36±7.15	24.76±3.6	NA	NA	NA	NA	5.4±0.5	6±0.3	5.5±0.6	1.4±0.4	3.7±0.6	1.5±0.5
Zhang et al A,[55] 2013	Healthy	31 (48)	47.87±10.95	23.9±2.1	124±8	79±5	94±6	NA	4.8±1.1	NA	4.7±0.4	1.4±0.3	2.9±0.4	1.3±0.3
De Marchi et al,[33] 2012	Healthy	34 (50)	32.4±3.5	19±3	119±4	79±9	92±7	34.8±6.6	5.1±0.6	NA	4.3±0.7	1.5±0.2	NA	1.5±0.1
Grassi et al,[35] 2012	Healthy	12 (58)	28±2.7	23.2±4.2	NA	NA	NA	NA	4.2±0.4	NA	NA	1.5±0.4	2.5±0.4	0.7±0.3
Suzuki et al,[49] 2012	Healthy	14 (57)	33.4±11.9	20.7±2.3	106±9	64±6	78±7	NA	4.8±0.6	5.4±0.3	5±0.6	1.7±0.4	2.7±0.5	0.8±0.4
Ceriello et al A,[28] 2011	Healthy	12 (50)	50.5±8.66	28.5±10.7	117±19	78±8	91±11	73.4±15.2	4.5±1.4	4.8±0.7	4.5±2.1	1.4±0.7	2.5±1	0.9±0.7
Mah et al,[41] 2011	Healthy	16 (0)	21.6±3.2	28.7±NA	117±4	79±4	92±4	147±96	5.3±0.4	NA	3.6±0.7	NA	NA	NA
Watanabe et al,[53] 2011	Healthy	14 (43)	33.4±11.9	20.7±2.3	106±9	64±6	78±7	29.7±11.9	4.7±0.4	NA	5±0.6	1.7±0.4	2.7±0.5	0.8±0.4
Baynard et al A,[25] 2009	Healthy	10 (NA)	53±3.32	32.7±3.5	117±13	72±3	87±6	NA	4.6±0.3	5.2±0.4	5.2±1	1.3±0.3	3.2±0.95	1±0.3
Ceriello et al (1) A,[27] 2008	Healthy	22 (45)	50.5±11.73	28.5±14.5	117±26	78±10	91±15	NA	4.5±1.4	4.8±0.9	4.5±2.8	1.4±0.9	2.5±1.4	0.9±0.9
Ceriello et al (2) A,[26] 2008	Healthy	10 (40)	50.3±8.22	27.5±9.8	115±14	76±11	89±12	NA	4.5±1	4.8±0.6	4.8±1.9	1.4±1.6	2.4±1.3	0.9±1.6
Natali et al A,[45] 2008	Healthy	20 (70)	49±8.94	27.9±4	129±13	78±9	95±10	NA	5.3±NA	5.6±0.5	4.9±0.9	1.2±0.2	3.3±0.8	1.1±0.5
Weiss et al,[54] 2008	Healthy	13 (62)	48±17	24±2.2	114±14	66±7	82±10	NA	5.5±1.4	NA	NA	NA	NA	NA
Xiang et al (1) A,[57] 2008	Healthy	26 (46)	50±6	24.2±2.3	114±7	72±6	86±7	NA	4.6±0.5	NA	4.4±0.9	1.2±0.1	1.9±0.7	1.4±1.2
Xiang et al (2) A,[56] 2008	Healthy	17 (41)	39±12.37	24.1±6.6	115±20	68±12	84±15	NA	5.1±1.7	5.1±0.4	4.7±2.7	1.2±0.7	1.9±2.4	1.4±3.8
Xiang et al (2) B,[56] 2008	Healthy	15 (47)	40±11.62	23.7±7.4	111±20	24±7	53±12	NA	4.6±1.9	4.8±0.8	4.5±1.9	1.2±0.7	1.9±1.8	1.4±3
Dengel et al A,[31] 2007	Healthy	15 (53)	11.3±1.55	17.5±1.9	110±12	59±8	76±9	41.2±15.1	4.8±0.3	NA	3.8±0.8	1.2±0.3	2.3±0.6	0.8±0.4
Zhu et al,[60] 2007	Healthy	11 (0)	22.6±2.3	22.5±1.5	113±7	79±6	90±6	NA	5.2±0.2	NA	4±0.8	1.4±0.2	2.1±0.6	0.9±0.3
Arora et al A,[22] 2006	Healthy	10 (0)	27±NA	22.4±NA	122±NA	68±NA	86±NA	NA	4.8±NA	NA	4.1±NA	1.8±NA	2.2±NA	1.1±NA
Fujimoto et al,[32] 2006	Healthy	10 (0)	30±2	NA	111±12	65±8	80±9	NA	5.1±0.6	NA	4.3±0.7	1.2±0.3	NA	1.2±0.7
Tushuizen et al,[51] 2006	Healthy	17 (0)	25.4±3	23.6±1.8	116±8	75±7	89±7	33±10	4.8±0.3	5.1±0.2	4±0.6	1.4±0.2	2.2±0.6	0.8±0.3
Napoli et al,[44] 2004	Healthy	10 (40)	23±3.16	23.6±1.9	124±6	60±3	81±4	NA	5±NA	NA	NA	NA	NA	NA
Siafarikas et al,[47] 2004	Healthy	32 (66)	19.1±1.7	22.9±4.2	NA	NA	NA	NA	NA	5±0.3	4±0.8	1.3±0.4	2.2±0.7	1.2±0.7
Ihlemann et al,[36] 2003	Healthy	10 (40)	53±6.96	22.7±1.9	144±17	75±11	98±13	NA	NA	5.2±0.3	5.2±0.6	1.7±0.3	3.2±0.6	0.8±0.3
Bagg et al,[23] 2000	Healthy	10 (20)	26±6	22±2	111±10	65±8	80±9	34.2±11.4	5.2±0.3	NA	4.7±1	NA	NA	NA
Title et al,[50] 2000	Healthy	10 (40)	25.5±3.1	24±3	118±8	72±7	87±7	NA	5.3±0.7	NA	5.1±1.1	1.3±0.1	3.3±0.9	1.2±0.5
Kawano et al A,[38] 1999	Healthy	17 (35)	52.6±7.42	NA	NA	NA	NA	51.6±9.9	5±0.3	NA	4.9±0.4	1.2±0.1	3±0.4	1.5±0.2

(*Continued*)

Table 2. Continued

Study, Year of Publication	Health Status	n (% Women)	Age, y	BMI, kg/m²	Blood Pressure, mm Hg			Fasting Plasma Insulin, pmol/L	Fasting Plasma Glucose, mmol/L	HbA_{1c}, %	Cholesterol, mmol/L			Triglycerides, mmol/L
					SBP	DBP	MAP				Total	HDL	LDL	
Williams et al,[55] 1998	Healthy	10 (30)	33±6.32	NA	NA	NA	NA	NA	3.9±1.2	3.6±0.6	4.2±0.7	1.1±0.2	2.6±0.7	1±0.4
Lavi et al,[40] 2009	Obese	56 (0)	47.9±5.8	32.1±4.3	134±13	82±6	99±8	NA	5.4±0.2	NA	5.1±0.7	1.1±0.2	3.2±0.7	1.7±0.9
Dengel et al B,[21] 2007	Obese	16 (56)	10.1±1.6	19.3±6.4	120±12	65±8	83±9	61.6±33.2	4.8±0.2	NA	4.2±0.6	1.1±0.2	2.6±0.5	1±0.6
Wang et al B,[52] 2013	IGT	33 (64)	52.88±9.2	27.8±3.1	NA	NA	NA	NA	6.1±0.5	6.5±0	5.5±1	1.2±0.3	3.1±0.8	1.8±0.9
Natali et al B,[45] 2008	IGT	16 (63)	52±20	29.5±4.8	122±12	79±8	93±9	NA	5.7±NA	5.9±1.2	5.6±1.4	1.3±0.5	3.7±1.3	1.3±0.6
Xiang et al (1) B,[57] 2008	IGT	21 (48)	51±6	24.8±3.1	110±8	72±6	85±7	NA	5.9±0.9	NA	5.2±1.1	1.2±0.2	2.3±0.7	2±1.1
Arora et al B,[22] 2006	IGT	10 (0)	65±NA	23.2±NA	134±NA	72±NA	93±NA	NA	5.3±NA	NA	4.3±NA	1.2±NA	2.1±NA	2.6±NA
Kawano et al B,[33] 1999	IGT	24 (38)	58.5±7.84	NA	NA	NA	NA	66±11.8	5.8±0.8	NA	5.3±1	1.1±0.1	3.4±0.5	1.7±0.2
Wang et al C,[52] 2013	T2DM	43 (42)	53.4±8.99	25.7±2.9	NA	NA	NA	NA	7.5±1.2	7.4±0.1	5.8±1.7	1.2±0.3	3.2±0.7	2.2±1.2
Ceriello et al B,[26] 2011	T2DM	16 (44)	51.3±10.4	29.5±13.2	123±26	80±14	95±18	107.3±15.2	7.8±8.8	8.4±1.2	5.1±3.2	1.2±0.3	2.6±0.4	1.2±1.6
Chittari et al,[29] 2011	T2DM	21 (43)	46.4±9.62	30.1±5	NA	76±8	NA	NA	7.8±1.8	7.8±1.4	4.5±0.9	1.2±0.5	2.5±0.9	1.6±0.5
Kato et al A,[37] 2010	T2DM	10 (50)	68±7.7	26.8±3.2	144±29	89±19	107±22	45±17.4	6.1±0.8	5.8±0.6	5.5±0.4	1.4±0.3	3.5±1.3	1.5±0.1
Kato et al B,[37] 2010	T2DM	10 (30)	67.6±6.2	25.8±2.5	141±26	88±23	106±24	57.6±33.6	6.1±1	6±0.3	5.2±0.7	1.5±0.3	3.7±1.8	1.3±0.2
Kato et al C,[37] 2010	T2DM	10 (30)	67.8±8.6	25.8±3.3	141±29	88±12	106±17	39.6±24.6	6.6±1	6.1±0.6	5.3±0.7	1.4±0.3	3.9±2	1.4±0.2
Ceriello et al (1) B,[27] 2008	T2DM	27 (48)	51.3±13.51	29.5±17.2	123±33	80±19	95±24	NA	7.8±11.4	7.7±1.6	5.1±4.2	1.2±0.3	2.6±0.4	1.2±1.6
Ceriello et al (2) B,[26] 2008	T2DM	10 (50)	50.3±6.96	27.5±10.1	118±17	77±12	91±14	NA	6.8±7	7.3±1	5±2.5	1.3±0.2	2±0.5	1±1.9
Ceriello et al (2) C,[26] 2008	T2DM	10 (50)	50.2±14.23	28.4±13	121±7	79±9	93±8	NA	7.7±1.3	7.9±1.6	5±2.2	1.2±0.3	2.7±0.4	1.3±0.95
Ceriello et al (2) D,[26] 2008	T2DM	10 (60)	51±17.71	28.6±11.7	122±11	80±12	94±12	NA	6±1	7.7±1.9	5.1±2.9	1.2±0.3	2.6±0.8	1.2±2.2
Natali et al C,[45] 2008	T2DM	17 (71)	58±8.25	29.3±4.1	139±17	81±8	100±11	NA	8.3±NA	7.2±2.1	4.9±1.2	1±0.3	3.29±1.1	1.5±0.4
Stirban et al,[48] 2006	T2DM	13 (NA)	56.9±10.1	30.3±3.2	136±22	79±13	98±16	NA	NA	8.5±1.8	NA	NA	NA	NA
Kim et al,[23] 2003	T2DM	8 (50)	55.9±3.7	25.4±3.2	134±7	82±6	99±7	NA	7.2±2.6	6.6±0.8	5.5±0.3	1.3±0.2	NA	2.1±0.6
Kawano et al C,[33] 1999	T2DM	17 (29)	62.2±4.95	NA	NA	NA	NA	84±22.3	7.1±0.3	NA	5.6±0.4	1.1±0.1	3.7±0.4	1.9±0.2
Shige et al,[46] 1999	T2DM	7 (29)	49.3±8	26±5	128±9	72±9	91±9	47.4±16.8	7.1±1.3	NA	4.9±13	1±0.2	NA	1.6±0.6
Zhang et al B,[59] 2013	Hypertensive	34 (50)	47.44±10.96	24.7±3.5	156±9	96±8	116±8	NA	4.7±0.6	NA	4.7±0.5	1.3±0.2	3±0.4	1.3±0.3
Zhang et al A,[58] 2012	Hypertensive	26 (50)	47.92±8.05	24.6±2.6	160±8	97±6	118±7	NA	5.3±0.5	NA	4.7±0.6	1.4±0.3	2.6±0.4	1.4±0.2
Zhang et al B,[58] 2012	Hypertensive	34 (47)	49.29±8	24.8±2.5	159±9	99±6	119±7	NA	5.2±0.6	NA	4.9±0.5	1.3±0.3	2.7±0.5	1.3±0.3
Ballard et al,[24] 2013	MetS	19 (26)	28.5±9.59	35±3.9	125±11	85±8	98±8	55±25.7	6±0.9	NA	4.7±0.9	1±0.1	2.8±0.2	1.9±0.9
Baynard et al B,[25] 2009	MetS	11 (NA)	52±3.16	34.4±5	123±7	78±3	93±4	NA	6.1±1.3	5.9±1.1	5.1±1	1±NA	3.1±0.7	2.4±1.3
Dye et al,[42] 2012	T1DM	11 (36)	14.5±3.32	21.5±9.6	105±7	61±10	76±9	NA	NA	8.3±1.2	NA	NA	NA	NA

Data are expressed as mean±SD or n. Some studies presented multiple health groups comparing normoglycemia and acute hyperglycemia vascular function and were therefore evaluated as individual studies (distinguished by A, B, C, or D). Authors who published multiple studies in a single year were distinguished by (1) or (2). BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; MAP, mean arterial pressure; MetS, metabolic syndrome; NA, data not available; T1DM, type 1 diabetic mellitus; T2DM, type 2 diabetic mellitus; and SBP, systolic blood pressure.

Table 3. Effect of Acute Hyperglycemia on Vascular Function in Healthy and Cardiometabolic Populations: Quality of Evidence

Outcome Among Participants	Design (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations*	Quality of Evidence (GRADE)
Decreased EF	RCT (23)	Serious†	Not serious	Not serious	Not serious	Publication bias likely¶	Low
Decreased EF	OBS (16)	Not serious	Not serious	Not serious	Not serious	None	Low
Decreased macro-EF	RCT (19)	Serious†	Not serious	Not serious	Not serious	Publication bias likely¶	Low
Decreased macro-EF	OBS (11)	Not serious	Not serious	Not serious	Not serious	None	Low
Preserved micro-EF	RCT (4)	Very serious†	Serious§	Not serious	Very serious‖	Publication bias likely¶	Very low
Preserved micro-EF	OBS (5)	Serious‡	Not serious	Not serious	Serious‖	None	Very low
Preserved VSMF	RCT (3)	Serious†	Not serious	Not serious	Not serious	None	Moderate
Preserved VSMF	OBS (3)	Not serious	Not serious	Not serious	Not serious	None	Low

EF indicates endothelial function; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OBS, observational study; RCT, randomized controlled trial; and VSMF, vascular smooth muscle function.

*Large magnitude of effect, dose–response, plausible biases decreasing the magnitude of effect, publication bias.

†Method for allocation of concealment and participant/assessor blinding is unclear or not performed. Incomplete outcome data and selective reporting when assessing endothelial, macrovascular endothelial, microvascular endothelial, and vascular smooth muscle function during acute hyperglycemia.

‡No control population included, failure to adequately control for confounding, and incomplete follow-up when assessing microvascular endothelial function.

§Large I^2 and point estimates vary widely across studies assessing microvascular endothelial function suggesting benefit, harm, and no effect of acute hyperglycemia.

‖The 95% confidence interval of the pooled risk ratio includes both positive and negative effects of acute hyperglycemia.

¶Publication bias is strongly suspected because of the presence of asymmetry in funnel plots for randomized control trials assessing endothelial, macrovascular endothelial, and microvascular endothelial function during hyperglycemia.

Discussion

To our knowledge, this is the first systematic review and meta-analysis to assess the effect of acute hyperglycemia on vascular function. Data from 39 studies assessing endothelial function alone or in combination with VSM function during acute hyperglycemia in healthy and cardiometabolic diseased individuals were pooled and analyzed. The meta-analysis provided evidence that the average effect of acute hyperglycemia on endothelial function is decreased function, whereas VSM function was preserved in healthy and diseased individuals. Because of evidence of heterogeneity, the interpretation of the pooled effects of hyperglycemia on endothelial function should be made cautiously. Considerable heterogeneity was identified for most subgroups suggesting that the variability across studies was because of not only sampling variability but also differences in treatment effect within each study.[61] Nevertheless, the large effect sizes and 95% CIs consistently favored normoglycemia, providing evidence of treatment effect.[64] Exploration of heterogeneity with metaregression indicated that the variability across studies could be explained by differences in age, blood pressure, and low-density lipoprotein cholesterol and the postocclusion interval of vascular assessment.

Currently, there is no consensus on the effect of acute hyperglycemia on endothelial function and VSM function as studies assessing vascular function during acute hyperglycemia have presented confounding results. This meta-analysis demonstrated evidence of macrovascular endothelial dysfunction during acute hyperglycemia in healthy people, as well as cardiometabolic diseased subjects, suggesting that the pathogenesis of CVD may begin, among others, with acute hyperglycemia-mediated transient decreases in endothelial function long before the onset of morbidities, such as obesity, hypertension, or type 2 diabetes mellitus. Interestingly, the inverse

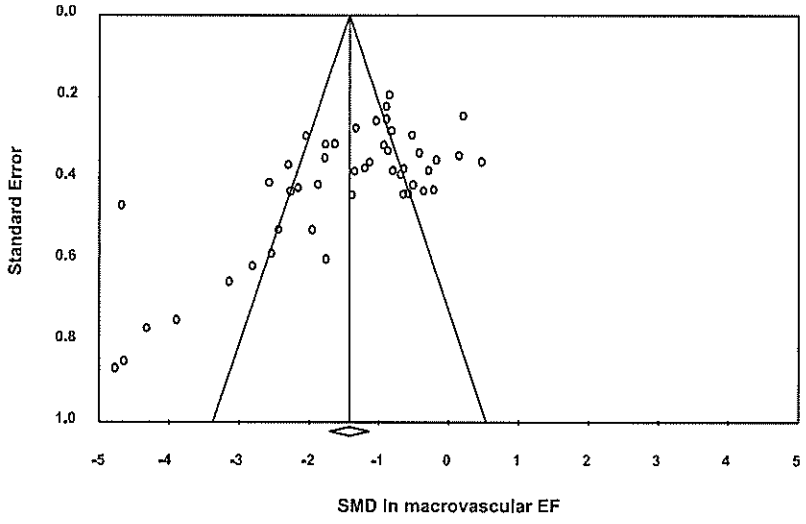

Figure 2. Funnel plot of the standardized mean difference (SMD) in macrovascular endothelial function in studies included in the meta-analysis. Funnel plot asymmetry: P=0.0002 and P=0.00005 according to Begg and Mazumdar rank correlation test and Egger test, respectively. EF indicates endothelial function.

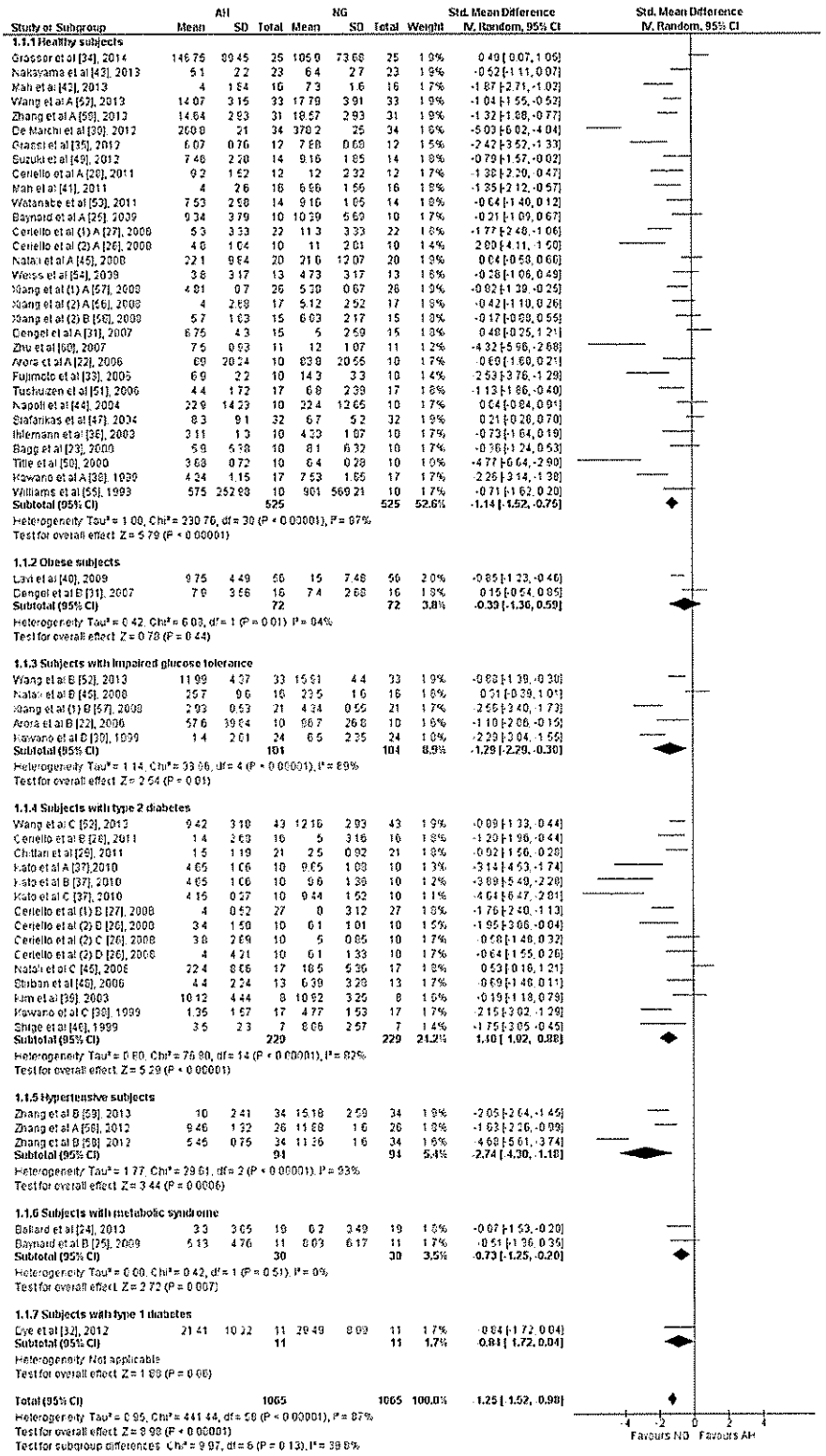

Figure 3. Forest plot of standardized mean difference (SMD) in endothelial function between acute hyperglycemic and normoglycemic states for all health groups included. Squares represent the SMD in endothelial function of each study. The diamond represents the pooled SMD in endothelial function by health group and overall. Some studies presented multiple subgroups according to health status; thus, they were evaluated as individual studies (distinguished by A, B, C, or D). Authors who published multiple studies in a single year had studies distinguished by numeric values (1 and 2). AH indicates acute hyperglycemia; CI, confidence interval; IV, inverse variance; and NG, normoglycemia.

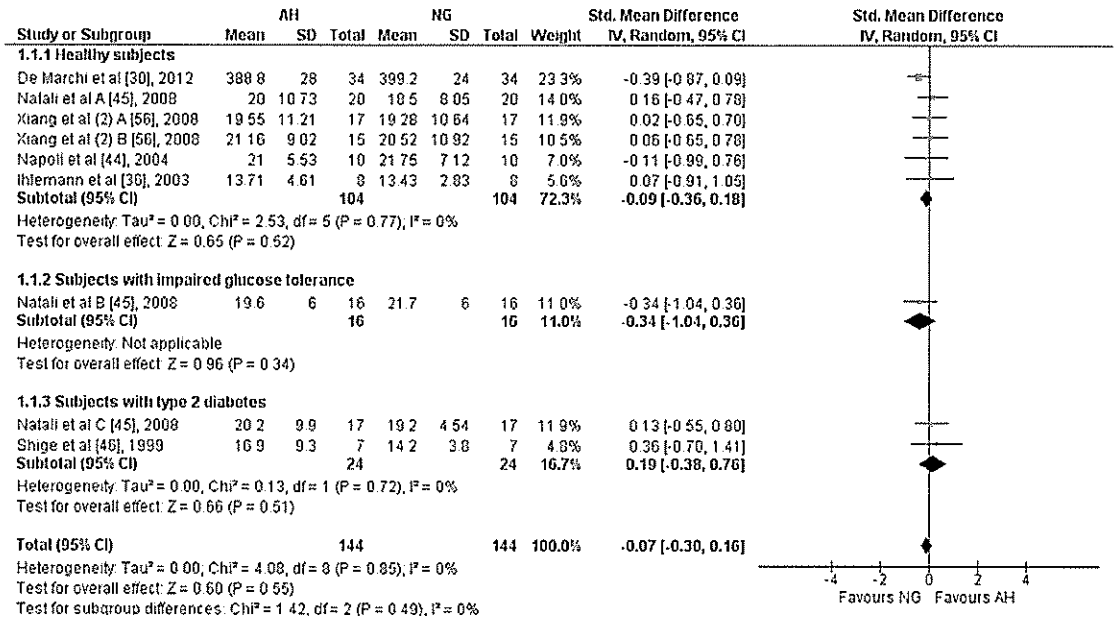

Figure 4. Forest plot of standardized mean difference (SMD) in vascular smooth muscle (VSM) function between acute hyperglycemic and normoglycemic states for all health groups included. Squares represent the SMD in VSM function of each study. The diamond represents the pooled SMD in VSM function by health group and overall. Some studies presented multiple subgroups according to health status; thus, they were evaluated as individual studies (distinguished by A, B, or C). Authors who published multiple studies in a single year had studies distinguished by numeric values (1 and 2). AH indicates acute hyperglycemia; CI, confidence interval; IV, inverse variance; and NG, normoglycemia.

relationship between macrovascular endothelial function and several traditional cardiovascular risk factors demonstrates the degree to which acute hyperglycemia mediates macrovascular endothelial dysfunction and correlates with increases in age, blood pressure, or low-density lipoprotein cholesterol levels. This is consistent with previous research revealing that elderly, hypertensive and subjects with dyslipidemia all exhibited significantly decreased endothelium-dependent vasodilation at rest compared with healthy populations,[65–67] indicating that any existing macrovascular endothelial dysfunction may therefore be compounded by an acute hyperglycemic stress. The fact that microvascular endothelial dysfunction during acute hyperglycemia was not detected contradicts previously published data that associates decreased microvascular function with incident type 2 diabetes mellitus and suggests a role for microvascular dysfunction in the pathogenesis of type 2 diabetes mellitus.[68] Although in this meta-analysis, macrovascular endothelial function was affected across healthy and cardiometabolic health groups, VSM function remained preserved during acute hyperglycemia when compared with normoglycemia. In contradiction to previous findings in animal and in vitro studies, which found VSM dysfunction mediated by VSM cell proliferation may occur in as little as 6 hours.[20,52]

Macrovascular endothelial dysfunction observed during acute hyperglycemia by methods assessing endothelium-dependent vasodilation primarily implicate decreased NO bioavailability as a central mechanism of endothelial dysfunction in healthy and cardiometabolic diseased populations.[69] This may be attributed to acute hyperglycemia increasing oxidative stress and its role in disrupting pathways of NO synthesis.[12] The fact that even healthy people exhibited decreased macrovascular endothelial function during acute hyperglycemia demonstrates how acutely NO bioavailability may be affected by excess sugar consumption. The magnitude of macrovascular endothelial dysfunction induced by acute hyperglycemia may be compounded when cardiovascular risk factors, such as increased age, blood pressure, or low-density lipoprotein cholesterol, are present. This may be partly due to the fact that health groups exhibiting these clinical markers demonstrate decreased NO bioavailability and therefore impaired endothelial function, even at rest.[65–67] Although NO is the predominant vasodilator in macrocirculation, it has been demonstrated to have significantly less influence in the microcirculatory system.[70] The increased influence of other chemical mediators of vasodilation, such as endothelial-derived hyperpolarizing factor and prostaglandin I_2,[71] may, however, explain why microvascular endothelial function remained preserved during acute hyperglycemia. Consideration should also be given to the spatial variability associated with the techniques used in several of the studies using skin microcirculation as a model of assessing microvascular function.[72] The large spatial variability in single-point laser Doppler flowmetry, for example, may have limited findings.[73] Despite this, final conclusions on the effect of acute hyperglycemia on microvascular function should not be made because of the limited availability of microcirculation data. Furthermore, it must be acknowledged that shear stress was not considered when performing analyses of flow-mediated dilation data in many studies. Shear stress, which is responsible for inducing the NO release that causes flow-mediated dilation, is dependent on variability of the hyperemic blood flow response in the microcirculation.[74]

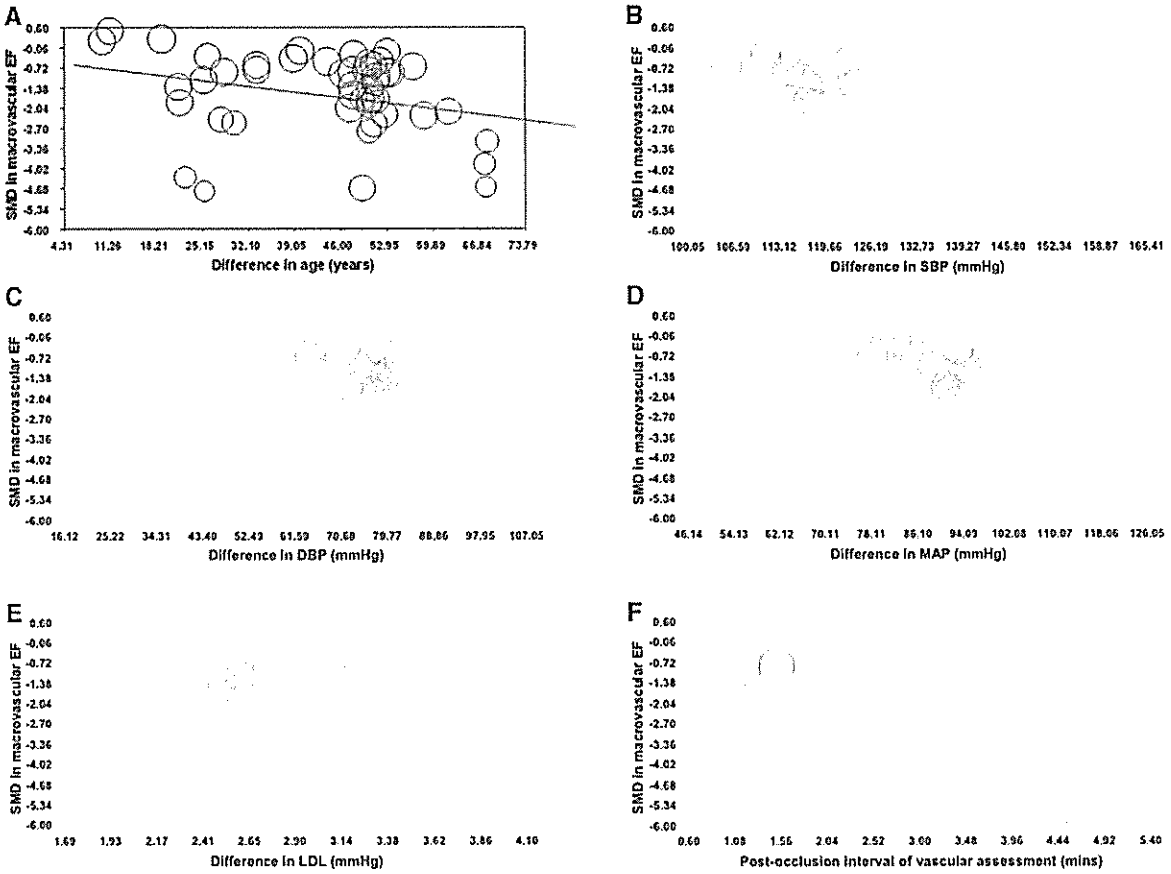

Figure 5. Metaregression plots of standardized mean difference (SMD) in macrovascular endothelial function (EF) according to the difference in (A) age (β=−0.03; *P*=0.005), (B) systolic blood pressure (SBP; β=−0.04; *P*=0.0004), (C) diastolic blood pressure (DBP; β=−0.05; *P*<0.00001), (D) mean arterial pressure (MAP; β=−0.05; *P*=0.00001), (E) low-density lipoprotein cholesterol (LDL; β=−0.93; *P*=0.005), and (F) postocclusion interval of vascular assessment (β=0.36; *P*=0.01). The size of each circle is proportional to the study's weight.

Therefore, macrovascular endothelial dysfunction observed during acute hyperglycemia may partially be mediated by a decrease in shear stress stimulus reflecting microvascular dysfunction.[74] The fact that VSM function was preserved during acute hyperglycemia indicates that endothelial dysfunction precedes VSM dysfunction, further supporting its role as a primary mechanism of CVD pathogenesis. Although disruptions in NO bioavailability mediated by acute hyperglycemia and the resulting endothelial dysfunction may initially be transient, if repeated often enough, they may lead to cumulative adverse outcomes, including proinflammatory responses and VSM cell proliferation.[12,75] It has been suggested that acute hyperglycemia may induce VSM cell proliferation by disrupting VSM cell apoptosis, which is a key mechanism to prevent increased neointimal formation and stenosis.[19] Moreover, decreased NO delivery by the endothelium to the VSM may contribute to VSM cell proliferation through increased periods of higher vasoconstrictive tone.[75] Ultimately, VSM cell proliferation may signal the beginning of a detectable and significant VSM dysfunction, representing a critical event in vascular remodeling and the development of CVD.[76]

Given that CVD is the single leading cause of death, accounting for 30% of the annual global mortality rate,[77] and that even healthy populations are subject to vascular dysfunction during acute hyperglycemia, there is a clear need to further investigate the effects of acute hyperglycemia on the underlying mechanisms of vascular function in vivo. Because of a surge in added sugar consumption in recent decades, predominantly in the form of sugar-sweetened beverages,[2] humans are more often in a state of acute hyperglycemia and therefore are more frequently inducing endothelial dysfunction. Considering this, future research should quantify what frequency and dosage of sugar consumption mediate atherosclerotic vascular changes in healthy and cardiometabolic diseased populations. Previously, certain ethnicities have demonstrated decreased vascular function at rest compared with white subjects.[78] Whether this exacerbates any vascular dysfunction mediated by acute hyperglycemia is still unknown and requires further research. To provide more comprehensive conclusions on how macrovascular and microvascular functions are affected by acute hyperglycemia, future research should consider shear stress as a covariate of conduit artery flow-mediated dilation data during statistical analyses.[79,80] Furthermore, noting that vascular function is not entirely mediated by NO,[12] future research may also investigate the effect of sugar-sweetened beverage consumption on numerous mechanisms of vasodilation (eg, NO, endothelium-derived

hyperpolarizing factor, and prostaglandin I_2) and vasoconstriction (eg, endothelin-1), the influence of which varies from microcirculation to macrocirculation.

There are many inherent limitations to our analyses that require comment. As previously discussed, significant heterogeneity was observed among studies that assessed endothelial function. Studies published in languages other than English were not included, and the quality of evidence for outcomes assessed in this meta-analysis was low-to-moderate. Subanalyses of microcirculatory and VSM data were limited because of the low number of studies assessing microvascular and VSM function in normoglycemic and acute hyperglycemic states. Furthermore, some studies used methods of assessing microcirculation that can be easily influenced by spatial variability and thus may limit results when assessing microvascular function. The risk of publication or other biases was detected when assessing the SMD in endothelial function. However, the quality of studies was evaluated by specific tools for the quality assessment of observational research,[81,82] revealing a predominantly low-bias risk. It must be acknowledged that the ethnicity of the populations was poorly reported by studies included in this meta-analysis, and thus, conclusions on the effect of ethnicity cannot be drawn from these data. Finally, many studies using flow-mediated dilation as a method of assessing macrovascular endothelial function did not report shear stress. Therefore, it was not possible to comprehensively conclude whether macrovascular endothelial dysfunction found during acute hyperglycemia is because of intrinsic abnormalities of macrovascular endothelial function or if it is partially attributable to microvascular dysfunction and decreased stimulus for conduit artery dilation.[79]

In conclusion, based on studies included in this meta-analysis, current evidence suggests that acute hyperglycemia decreases macrovascular endothelial function with no changes in microvascular endothelial function and systemic VSM function across healthy and cardiometabolic populations. This further supports endothelial dysfunction mediated by decreased NO availability as a primary mechanism in the pathogenesis of CVD, which may begin long before vascular remodeling is detectable or the onset of cardiometabolic diseases. Noting that microvascular data were limited, the microcirculatory system should therefore not be dismissed as a possible site of vascular dysfunction. Considering this, future studies should investigate the effects of sugar-sweetened beverage consumption on the underlying mechanisms of human vascular function at microvascular and macrovascular levels. These studies will provide a better understanding of how acute hyperglycemia induces vascular dysfunction and how it contributes to the pathogenesis of CVD from healthy to cardiometabolic populations.

Acknowledgments

G. Walther was responsible for the concept and design of the study. Acquisition of data was carried out by J. Loader, D. Montero, C. Lorenzen, and G. Walther. J. Loader, D. Montero, and G. Walther analyzed and interpreted the data. Drafting of the article was carried out by J. Loader, D. Montero, and G. Walther. J. Loader, D. Montero, C. Lorenzen, R. Watts, C. Méziat, C. Reboul, S. Stewart, and G. Walther critically revised the article for important intellectual content. D. Montero provided statistical expertise, and J. Loader, D. Montero, C. Lorenzen, R. Watts, S. Stewart, and G. Walther provided administrative, technical or material support. All authors approved the final version of the article.

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Disclosures

None.

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Significance

Acute hyperglycemia has previously been proposed to contribute to vascular dysfunction, which represents one of the main precursors to CVD. However, the effect of acute hyperglycemia on mechanisms of vascular function in humans is unclear because of discrepant results. Given this, we conducted the first systematic review and meta-analysis of its kind comparing endothelial function alone or in combination with VSM function during acute hyperglycemia in healthy and cardiometabolic diseased individuals. We demonstrate that acute hyperglycemia transiently impairs macrovascular endothelial function, which may represent, among others, a primary mechanism in the pathogenesis of CVD. This is significant when considering the surge in added sugar consumption in recent decades; humans are more often in a state of acute hyperglycemia and therefore are more frequently inducing endothelial dysfunction. This study provides the foundation for future research that will investigate the effect of acute hyperglycemia on underlying mechanisms of vascular function.